When autologous vein is unavailable, prosthetic graft materials, particularly expanded polytetrafluoroethylene are used for peripheral arterial revascularisation. Poor long term patency of prosthetic materials is due to distal anastomotic intimal hyperplasia. Intimal hyperplasia is directly linked to shear stress abnormalities at the vessel wall. Compliance and calibre mismatch between native vessel and graft, as well as anastomotic line stress concentration contribute towards unnatural wall shear stress. High porosity reduces graft compliance by causing fibrovascular infiltration, whereas low porosity discourages the development of an endothelial lining and hence effective antithrombogenicity. Therefore, consideration of mechanical properties is necessary in graft development. Current research into synthetic vascular grafts concentrates on simulating the mechanical properties of native arteries and tissue engineering aims to construct a new biological arterial conduit.

Keywords: Intimal hyperplasia; Vessel wall mechanics; Compliance; Porosity; Compliance mismatch; Polytetrafluoroethylene; Polyurethane; Vascular graft; Infrainguinal bypass; Graft caliber; Anastomosis.

Introduction

Infrainguinal arterial bypass is one of the key vascular procedures, with 12,810 revascularisation procedures carried out in 1993 in the United Kingdom and a lower limb critical ischaemia prevalence of 1 in 25001. Success is limited if a prosthetic graft is used or the distal anastomosis crosses the knee joint (Fig. 1). Where possible, autologous long saphenous vein is used2; however, this is not available or suitable in a significant proportion of cases. Arm veins may be used with primary patency of 60–85% at 3–5 years3, the difference with saphenous vein being attributable to previous venepuncture, phlebitis, oversized diameter, a propensity towards phlebitis and aneurysmal dilatation. Human umbilical vein grafts have a higher patency rate than prosthetic alternatives, but are prone to aneurysm formation in the long term and their use has not been widespread4. Cryopreserved allografts have 1-year patency rates of only 52%5 with the additional complications of immunoreaction and proximal post-anastomotic stenosis. Good patency rates using deep vein segments are possible6 with 89% secondary patency at 3 years in selected patients7, but the surgery is difficult and prolonged due to the need for extensive dissection at proximal and distal anastomotic sites; also the risk of severe venous oedema as a result of venous outflow obstruction8 has meant that this approach has never been in favour. The main prosthetic materials developed for bypass grafting are polyethylene terephthalate (Dacron) and polytetrafluoroethylene (PTFE). Dacron is manufactured into a woven corrugated graft that is suitable for high flow large vessel segment replacement, such as diseased aorta replacement. However, recent randomized controlled trials9 have shown Dacron to be as good as PTFE for infrainguinal bypass. PTFE has achieved widespread use as a smaller diameter
tubular graft. In above knee femoropopliteal revascularisation, individual groups have published data to suggest that the patency rates when using PTFE are not significantly different to that for saphenous vein.10,11 However, these studies lack power and a meta-analysis showed that at every point in time, the patency was greater when autologous saphenous vein was used.2

Small diameter grafts (<6 mm) are especially liable to blockage and research into the causes of this failure and possible alternative materials with properties more akin to the original artery has been undertaken in recent times.

Between 2 and 24 months after bypass grafting, intimal hyperplasia (IH) is responsible for poor patency.12 Vascular endothelial cell damage triggers IH formation. The postulated reasons for IH are mechanical; the difference in compliance between native vessel and graft; change in direction of flow at the anastomosis; luminal diameter difference at the anastomosis; vessel wall damage and suture technique. Interposing an autologous vein cuff making the compliance mismatch more gradual, redistributes IH away from the most critical areas of the anastomosis, principally the heel, the toe and recipient artery floor,13 leading to some improvement in patency but keeping the overall extent of IH unchanged.

Fluid dynamic studies reveal how endothelial damage may result from compliance mismatch. The cells are directly affected by altered stresses of blood flow through the anastomosis, known as wall shear stress (WSS). Even within the human arterial system, the shear stress varies between different vessels14 with superficial femoral artery mean wall shear rates of 130 s⁻¹ compared with a carotid value of 333 s⁻¹. WSS also varies depending on physiological conditions such as exercise. Experimental evidence suggests both high and low shear stress cause IH. One explanation for this is that it is the resultant flow pattern changes rather than the shear stress itself that causes IH. Such changes in shear stress include divergent flow associated with low shear stress resulting in flow separation, rarefaction and increased oscillatory shear. On the other hand, there is convergent flow associated with high shear stress, which is responsible for endothelial cell injury.

The research into alternatives to ePTFE and Dacron has concentrated on new materials with viscoelastic properties similar to native artery, principally polyurethane due to its compliance and favourable biocompatibility. This review aims to discuss the critically important roles mechanical properties such as viscoelasticity and haemodynamics play in maintaining patency of infrainguinal bypass grafts.

**Basic Mechanical Theoretical Considerations**

Poiseuille’s law states that the pressure drop in a tube (P) is directly proportional to the tube length (L), the rate of flow (Q) and the viscosity (η), and inversely proportional to the fourth power of the internal radius (r_i) of that tube.

\[ P = \frac{KLQ\eta}{r_i^4} \]  \hspace{1cm} (1)

Substituting the Ohm’s law analogy which states that \( P = RQ \) (\( R \) = impedance) and the value of \( K \), calculated experimentally:

\[ R = \frac{8\eta L}{\pi^2 r_i^4} \]  \hspace{1cm} (2)

Therefore, when considering bypass conduits, the impedance to flow is drastically increased by reducing graft calibre, thereby reducing flow rate and increasing the risk of stasis and so promoting thrombogenicity. However, these equations relate only to pure laminar flow in a rigid pipe—every particle is moving parallel to the axis of the tube with a constant velocity. Within one lamina, all particles will have the same velocity and moreover, laminae near the centre of the tube have greater velocity than more peripheral ones, giving a parabolic flow profile (Fig. 2).

These theoretical considerations do not hold true completely in the arterial system for numerous reasons. First, the artery is not a rigid pipe. It is a
complexly compliant structure with intrinsic and extrinsic mechanisms to vary compliance and shape, and in so doing, contributing to the pressure for flow itself. Next, blood flow only approaches laminar flow in the largest arteries. Even in these vessels, the rate of flow is not steady and it is only in diastole and early systole that laminar flow is observed. Turbulent flow due to branching vessels is also widespread. Blood is a non-Newtonian fluid, being a suspension of particles of various sizes. This makes its behaviour unpredictable, especially in small diameter vessels.

Nevertheless the laminar model can be used to describe useful concepts in the investigation and description of the mechanical properties of blood vessels and flow. One such model is WSS.

The resistance $R$ in Poiseuille’s formula relates to the impedance to flow of a particle in one lamina caused by the friction of the adjacent lamina. In the same way, at the most peripheral lamina there is a force exerted by the particles flowing here on the wall of the vessel itself. This action against the wall is termed WSS. Therefore, when considering the vessel wall;

$$WSS = R = \frac{8\eta L}{\pi r^4}$$

(3)

The tendency for deformation of the vessel wall due to pulsatile flow of blood through it is, within physiological limits, elastic. This is to say that if the blood force is removed, the vessel will return to its previous shape. However, the force does not cause an instantaneous deformation, like when a weight is placed on a spring. The shape change, in the presence of a constant force is a gradual one and the same is true when the force is removed. This property of delay is termed viscosity. The blood vessel demonstrates a combined viscoelastic tendency.

Overall the mechanical behaviour of an artery is complex. The ideal graft for anastomosis would replicate this behaviour. In order to simplify the investigation and description of this behaviour in arteries and graft materials, the term ‘compliance’ is used, encompassing the changing mechanical properties depending on the haemodynamic pressure within the graft, unlike established physical concepts such as Young’s modulus, $E$. At a given pressure $P$ in a vessel of diameter $d$ and wall thickness $t$:

$$E = \frac{\text{stress}}{\text{strain}} = \left( \frac{Pd^2t}{2Ad} \right)$$

(4)

Rearranging this:

Compliance $= \frac{d}{2Et}$

(5)

Therefore, compliance is inversely proportional to vessel wall thickness. Manufacture of a synthetic graft with a thinner wall results in greater distensibility. Conversely, patients with peripheral vascular disease already have increased intima-media thickness, contributing to arterial rigidity.

The overall result of the viscosity of the arterial wall and its compliance (i.e. viscoelasticity) is to convert the pulsatile ejection of the heart into a continuous flow, storing a part of the energy of propulsion in systole and restoring it to the circulation during diastole. Therefore, viscoelasticity is important in energy transfer and dissipation. All vascular tissues have greater dimensions during unloading than during loading, leading to a ‘hysteresis loop’ when the pressure/diameter characteristics of the vessel are plotted on a graph (Fig. 3). The area within the loop represents the storage of energy in the vessel wall and so viscosity, which is modulated by the vascular endothelium. Investigations of the mechanical properties of arteries that have not specifically concentrated on viscosity have measured the phase delay between pulse pressure and distension. This method demonstrates viscosity when considering a single pulse of flow. However, in physiological pulsatile flow, the alternating storage and discharge of energy by the vessel wall leads to an intrinsic energy capacitance as well as a continuous loss of energy, which is more accurately measured from hysteresis loops.
Mechanical Properties of Bypass Grafts

Non-mechanical causes for IH in vascular bypass grafts include thrombogenicity; the absence of a vascular endothelium to produce chemical signals such as nitric oxide and non-biocompatibility.

There is widespread reporting that compliance mismatch, rather than geometric factors, is primarily responsible for IH and subsequent poor graft patency as a result of turbulent flow (Table 1).

Further flow disturbances are caused by injudicious choice of anastomosis angle or bypass conduit calibre at the time of surgery. Also, anastomotic stresses at the suture line lead to IH independent of compliance changes.

Compliance

It is the haemodynamic flow changes due to compliance differences across an anastomosis, which both cause increased shear stress to damage endothelial cells and also reduced shear stress leading to areas of relative stasis and increasing interaction between platelets and vessel wall; pooling of chemokine factors as well as increasing oscillatory forces. The aim of matching compliance is to minimise these disruptive flow characteristics.

The vortices created by compliance mismatch are further complicated by localised high compliance, 2–3 mm proximal and distal to the anastomotic line, termed the ‘perianastomotic hypercompliance zone’ (PHZ) (Fig. 4). This contributes to giving the overall perianastomotic region compliance properties somewhere in between those of artery and graft (Fig. 5). The artery’s J-shaped curve of compliance shown in Fig. 5 demonstrates how it does not obey Hooke’s law when subjected to pulsatile flow. This is due to highly elastic elastin fibres controlling its distension at low pressure flow and relatively inelastic collagen fibres taking over at higher pressures. At 100 mmHg only 5–6% of collagen fibres are recruited with progressive recruitment with rising pressure. Physiological influence causes recruitment of vascular smooth muscle cells in conjunction with some collagen fibres with elastin fibres bearing the remaining share of the stress.

Design of alternatives to PTFE has concentrated on achieving a compliant structure. This has been approached in several ways including porous ‘spongy’ materials and double tubular grafts with a more compliant inner lining and a less compliant outer layer. As these latter grafts are distended, they become progressively less compliant as the outer sleeve properties become more prominent. Our unit has produced and characterized porous compliant poly(carbonate)polyurethane (CPU) grafts (Myo-Link) (Fig. 6).

Another aspect of interest to graft designers is the long term change in compliance after implantation. The artery has an astonishing capacity to maintain its intrinsic compliance despite abnormal chronic physiological changes such as hypertension. This is observed to cause wall thickening but compliance is largely unaffected due to intrinsic changes in the vessel wall properties. Interestingly, when a vein graft is used, it undergoes wall thickening and does not lose its compliance properties. However,
the effect of the surrounding tissues on an implanted prosthetic graft is to reduce compliance with time. This is especially the case in porous structures with a pore size greater than 45 μm when considerable fibrous tissue ingrowth takes place.

Compliance measurement is achieved by the investigation of distension due to pressure changes within a conduit and a range of methods have been used as described in Salacinski et al’s recent review.32

Conduit Calibre

Poiseuille’s law shows that the pressure of flow for blood through a conduit is inversely proportional to the fourth power of its radius. When considering an implanted bypass graft with no side branches, a purposeful tapering of the graft would lead to a massive concentration of pressure across it.33 The natural tapering of the vasculature distally is workable without pressure increases due to extensive branching of the native vessels.

Treiman et al.’s34 duplex studies show that a larger diameter venous graft is associated with lower distal graft velocity. For above knee femoropopliteal35 and for coronary artery bypass,36 it has been confirmed clinically that larger diameter grafts confer better patency rates than smaller conduits. This explains how reduced flow velocity at the anastomotic floor of the Venaflo™ cuffed PTFE anastomosis prevents excessive shear stress, translating to reduced IH.37

High flow at the larger proximal anastomosis is partially protective as it allows for the rapid dispersal of chemotactic factors released due to endothelial injury. It is the smaller distal anastomosis where the majority of IH is seen. Here, particularly in an infragenicular bypass even a slight thickening of the intima will cause a considerable stenosis, compared with a large calibre vessel (Fig. 7). Stenosis promotes platelet adherence and thrombosis. A vein cuff or the Distaflo™ PTFE graft widens the distal anastomosis and both are used clinically with better patency than PTFE alone.38

Conversely, a grossly oversized distal conduit will result in a sudden decrease in flow rate with relative stasis and flow separation. The resultant low shear rate is associated with IH as discussed earlier. Hence, the ideal diameter difference between graft and artery at the distal anastomosis is a balance to maintain the ideal flow velocity and resist turbulent flow.

Anastomotic Line Stresses

The creation of an end-to-end (ETE) anastomosis itself reduces compliance at the suture line.39 A continuous suture technique causes a greater loss of compliance than interrupted sutures with greater concentration of stresses at the suture line tethering it against distension. Clips that do not penetrate the intima also results in an anastomosis with less compliance mismatch (CM).21

How Porosity Affects Mechanical Properties

The artery is a selectively permeable structure and a microporous architecture in a prosthesis has been shown to mimic arterial function.

Endothelialisation of the luminal aspect of a graft comes about directly from the artery edge at the anastomotic site as well as via fibrovascular infiltration from the surrounding tissues. It is this fibrovascular infiltration that allows speedy uniform lining of a long

Fig. 6. Variation of compliance vs. mean pressure for different conduits. The pulse pressure was 60 mmHg. CPU is a compliant prosthesis unlike ePTFE and Dacron.23

Fig. 7. Proportional cross-section area as a result of 1 mm graft stenosis. The consequence of a 1 mm graft stenosis is much greater in a small caliber vessel than in a large diameter conduit.
graft. Zhang et al.\textsuperscript{40} showed that with physiological pulsatile flow in an animal model, full ordered endothelialisation of a small diameter prosthesis is possible within 8 weeks, providing a pore size of 30 $\mu$m diameter. They also demonstrated that the external aspect pore size correlated with the rate of endothelialisation. White et al.'s\textsuperscript{41} review of pore size shows that the ideal pore size for fibrovascular infiltration is between 10 and 45 $\mu$m. However, larger pores allow too much surrounding fibrous tissue invasion risking a dramatic loss of compliance.\textsuperscript{42}

It has been showed that porous CPU promoted successful seeding of endothelial cells onto its surface.\textsuperscript{43} By isolating the effects of surrounding tissues and fibrovascular infiltration in a laboratory model, it has been showed that after initial seeding, a porous graft allows stronger endothelial cell adherence when exposed to pulsatile flow than smooth ePTFE.\textsuperscript{44} PTFE grafts with low porosity were explanted after a mean implantation time of 523 days, from human subjects and examined.\textsuperscript{45} It was found that cellular infiltration into the grafts was poor, with mostly thin patchy fibrin cover to the lumen.

Therefore, in the development of a new graft, the precise measurement of its porosity is critical. This has been addressed since 1961 when Wesolowski et al.\textsuperscript{46} used a machine to compress the graft wall and measure the rate of flow of water through the wall at a water pressure of 120 mmHg. They found this measure to be highly reproducible.

### The Importance of Burst Pressure

This relates to the pressure that the vascular conduit can be subjected to before an acute leak develops and the conduit fails. The maximum force, $f$, applicable to any material is represented by:

$$f = \frac{Prd}{2t}$$

where $P$, $d$ and $t$ are (burst) pressure, diameter and wall thickness, respectively.

Therefore, it can be seen that the burst pressure decreases with increasing diameter and with decreasing wall thickness, since $f$ is a finite entity. It is, therefore, very likely that the burst pressure for a small diameter graft will far exceed the physiological range of blood pressures possible in man. For example, the burst pressure of a typical carotid artery is in the region of 5000 mmHg and for a saphenous vein is around 2250 mmHg. Burst pressure of porous polyurethane grafts have been found to be 1850–2050 mmHg,\textsuperscript{47} again much greater than any possible physiological blood pressure.

### Aneurysmal Change

Elastin degradation, notably by matrix metalloproteinases (MMP) 2 and 9, initiates aneurysmal change in an artery. This serves to remove elastin’s stress buffering properties, transferring more force straight to collagen. The breakdown of type I collagen, mediated by MMP 8,\textsuperscript{48} ensures expansion and possible rupture of the aneurysm.

Aneurysmal change in PTFE is now a rare event, since reinforcement of PTFE grafts was introduced in 1977. Similarly knitted Dacron peripheral bypass prostheses have in the past occasionally become aneurysmal, due to initial yarn slippage and stretching,\textsuperscript{49} leading to material fatigue, fraying and breakage in association with biodegradation of the frayed fibres.\textsuperscript{50} This in turn has lead to excessive stress in adjacent fibres, which are taking an increased strain. However, modern manufacturing techniques have eliminated aneurysmal dilatation of Dacron.

The failure of a polyurethane graft to cope with cyclical circumferential stretching can be predicted from the order of magnitude of its experimentally derived burst pressure. However, the pressure at which aneurysmal dilatation occurs \textit{in vivo} is lower than the absolute burst pressure, with other contributing factors being the level of autologous tissue ingrowth to aid structural integrity externally; as well as biodegradation.

### Properties of Bypass Conduits in Clinical Use

#### Mechanical properties of autologous vein

Unlike the arterial system, veins do not have to deal with pressures greater than 75 mmHg and have a lower compliance range than arteries due to a lower collagen:elastin ratio and much less smooth muscle. Their role is to maximize capacitance rather than to contribute to pulsatile flow transmission. However, a venous graft anastomosed to an artery will suddenly overdistend to its limit. This will lead to immediate deendothelialisation.\textsuperscript{51} The sequence of events over the next 30 days is often termed ‘arterialisation’. This involves luminal wall platelet deposition; vascular smooth muscle cell (SMC) apoptosis and necrosis; monocytic infiltration; adventitial fibroblastic activity and angiogenesis; myointimal thickening with media
SMC proliferation and infiltration. Finally, there is reendothelialisation.

From 3 months onwards, considerable remodelling of a venous graft in situ has been shown to occur.52 There is wall thickening with concomitant reduction in wall tension; lumen size changes depending on the initial lumen size with lumens larger than 3.75 mm in diameter actually getting smaller; and a significant increase in wall stiffness. These changes along with reendothelialisation equip the graft for use as an arterial conduit. This is reflected in the sizeable failure rate for venous grafts in the 1st year compared with subsequent annual occlusion rates.53

Due to low elastin levels compared with an artery, the overdistension caused by arterial blood pressure gives the vein poor compliance properties, making it in effect a rigid tube. Stooker et al.54 found lower leg saphenous vein to be more distensible than its upper leg equivalent in the venous pressure range. Davies et al.55 found that compliance of a vein was inversely proportional to both circular muscle hypertrophy and focal hyperplasia, confirming that the thicker-walled distal saphenous vein segments show less compliance. However, this latter study was an in vivo investigation with the confounding effect of surrounding tissues on compliance.

**Mechanical properties of ePTFE**

ePTFE is very stable in vivo with no reported failures due to degradation of the graft.45 It is poorly compliant, made up of fibrils extruded into a tubular structure with moderate stiffness.32 Perivascular reaction reduces its compliance further to only 14% of its pre-implantation level. The gaps between the fibrils form micropores which are so small (<0.05 μm) that many studies consider it to be a non-porous material.56 Because of this ePTFE grafts have very poor lumenal endothelialisation in vivo.45 Higher porosity can be conferred to PTFE by constructing a graft with a larger fibril size (60 vs. 20 μm) leading to the promotion of transmural tissue growth.57

**Mechanical properties of Dacron**

Polyethylene terephthalate or Dacron is composed of tightly woven or knitted fibres of very high tensile strength (10-fold that of PTFE).32 Individually, the microfibres are susceptible to slow hydrolytic degradation, but their highly crystalline ordered structure prevents this. The knitted graft is highly porous and the need for pred clotting may be avoided by presealing with gelatin or albumen. Crimping of the conduit or external reinforcement is required to prevent kinking, especially if the graft is to cross the knee joint. Initial unfavourable comparison with saphenous vein in peripheral bypass was in part due to the absence of antiplatelet therapy but modern trials suggest they are at least as good as PTFE for above-knee femoropopliteal bypass.9,58

**Prostheses of the future**

**Synthetic grafts**

The search for new compliant prostheses to replace ePTFE has concentrated on polyurethane materials25 due to their favourable biocompatibility. The fundamental building block for these polymers is a repeating sequence of urethane:

\[ \text{–NH(CO)O–} \]  \hspace{1cm} (7)

They consist of a hard segment and a soft segment to give strength and elasticity, respectively.

Polyurethane has yet to be used clinically as an infrainguinal bypass graft. Before this can occur, further research into compliant polyurethane development with particular consideration of anti-thrombogenic properties and endothelialisation in vivo is required. In addition, a host of different manufacturing processes have been identified and the most suitable one needs to be identified in terms of reproducibility and quality control.

**Tissue engineered grafts**

A biological arterial substitute incorporating the cellular layers of the native vessel can reflect the adaptable mechanical properties of the artery as well as providing its inherent antithrombogenicity. A biodegradable scaffold can provide a template on which the cellular components can align and the overall structure can mature with collagen being laid down potentially resulting in ideal mechanical properties in the long term.55 Such tubes achieve good burst and suture retention strength.60 Burst strength is increased by prolonging in vitro culture pre-implantation with the downside of compliance loss (Table 2).61

It is possible to create tissue engineered vessels without a scaffold by forming tissue around mandrels implanted subcutaneously62 or intraperitoneally.\(^5^3\) This technique uses the body’s own foreign body reaction to form a myofibroblast and collagen matrix which is robust enough to be implanted as a vascular prosthesis in that same body. Pulsatile flow causes matrix thickening with further collagen deposition and elastic lamellae formation; myofibroblast differentiation into

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SMCs along with their circular alignment. However, ultimately this technology requires an invasive procedure to implant a foreign body intraperitoneally in the recipient human. The consequences of infection would be very serious in patients with critical ischaemia especially since they are usually already at high medical risk.

Therefore, it would be desirable to construct a fully tissue-engineered graft made up of autologous cells ex vivo. L’Heureux’s group achieved burst pressures of 2954 ± 501 mmHg with a tubular structure made from coaxial sheets of cultured vascular SMCs and human fibroblasts which was seeded with endothelial cells. This was as a result of a well organized collagen matrix with parallel fibres in perpendicular bundles. Elastic fibres were also seen. The overall structure was macroscopically and microscopically similar to an artery.

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Mechanical Properties of Vascular Bypass Grafts


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